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Severe Sweet's Syndrome with Elevated Cutaneous Interleukin-1β after Azathioprine Exposure: Case Report and Review of the Literature

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Key Words
Azathioprine · Inflammatory bowel disease · Neutrophilic dermatosis · Sweet's syndrome · Interleukin-1β

Abstract
Sweet's syndrome (SS) is a dermatosis with systemic symptoms characterized by tender, red nodules or papules, occasionally covered with vesicles, pustules or bullae, usually affecting the upper limbs, face and neck. SS is frequently observed in patients with leukemia or connective tissue diseases, while it is rather seldom in patients with inflammatory bowel disease. The exact pathogenesis of SS is only partially understood. We report the case of a 50-year-old patient with indeterminate colitis, presenting with a febrile diffuse papulopustular and necrotizing skin eruption that healed with significant scarring and appeared 14 days after onset of treatment with azathioprine. Histological examination revealed the presence of features typical of SS, gene expression analysis very high levels of interleukin-1β (IL-1β) mRNA in lesional skin, and immunohistochemistry high levels of IL-1β at the protein level. SS associated with azathioprine is being increasingly reported and is reviewed herein.

Introduction

Sweet's syndrome (SS), or acute febrile neutrophilic dermatosis, belongs to the group of the so-called neutrophilic dermatoses and was first described in 1964 by Robert Douglas Sweet [1]. The cutaneous lesions of SS typically appear as tender, red or purple-red papules or nodules. They most frequently occur on the upper extremities, face and neck [2]. Less commonly SS can present as a pustular dermatosis [3]. Affected patients may appear dramatically ill. Fever and leukocytosis usually accompany the skin eruption. Several clinical conditions have been linked to SS. A probable association between the occurrence of the following conditions and the development of SS is considered likely: cancer (hematologic malignancies and solid tumors), infections (most commonly of the upper respiratory tract and the gastrointestinal tract), inflammatory bowel disease (IBD) (includes Crohn's disease and ulcerative colitis), medications (granulocyte colony-stimulating factor [G-CSF] as the most commonly reported medication), and pregnancy [2].

Various medications have been reported to induce SS, including G-CSF, antibiotics, retinoids, antiepileptics and antihypertensives. More recently azathioprine (AZA), the nitroimidazole of 6-mercaptopurine, which is widely used as a corticosteroid-sparing agent in a variety of autoimmune inflammatory diseases, has been increasingly reported as a potential cause of SS [4–14]. Here we report a severe case of SS associated with AZA therapy, review the literature concerning similar cases reported to date and analyze the expression of the proinflammatory cytokine interleukin-1β (IL-1β) in our patient's skin lesions.

Case Description

A 50-year-old male smoker was emergently referred to our department for an impressive febrile diffuse pustular and necrotizing skin eruption. He had a background history of a IBD, namely indeterminate colitis affecting the sigmoid colon that had first been diagnosed 5 months previously. Oral sulfasalazine therapy had been ineffective. Approximately 5 weeks prior to presentation, he had experienced a flare of his colitis managed with an oral medication of 50 mg prednisone daily. 14 days prior to presentation, AZA had been introduced at a dose of 50 mg once daily.

The patient's current illness began about 4 days prior to his transfer to our department. He initially developed a mac-

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Fig. 1. Florid cutaneous eruption of the upper torso, face and neck consisting of erythematous papulopustular lesions 2–10 mm in diameter, many of them with a central depression and/or erosion (**a**, **c**), evolving over time to central crusting (**b**).

Fig. 2. Large aphthous lesions with a fibrinous base on the hard palate.

ulopapular rash predominantly on the trunk, accompanied by high fever and fatigue. In the following days he developed a painful cutaneous eruption that was most marked over the upper back, shoulders, neck and face. This was accompanied by loose, partially bloody diarrhea with more than twenty bowel movements per day. There were no relevant symptoms pertaining to other organ systems. Upon arrival he was febrile (39.6°C), tachycardic (129 beats/min) and had a blood pressure of 116/84 mm Hg. Examination of the patient's skin revealed a florid eruption consisting of scattered well-delimited nummular erythematous papulopustular lesions 2–10 mm in diameter, many of which were depressed in the center (fig. 1). Fresh lesions were infiltrated erythematous plaques with a central pustule; older lesions were infiltrated erythematous plaques with a brown-colored central crust. The cutaneous eruption was mostly confined to the upper torso, face and neck, but the mucosa was also affected, with aphthous lesions 5–10 mm in diameter and a fibrinous base (fig. 2).

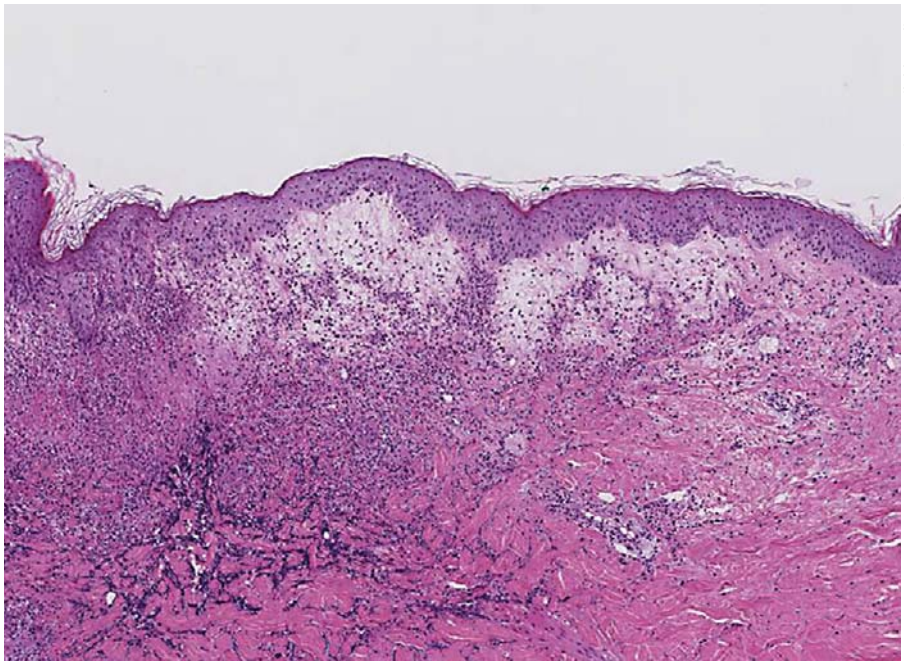
Laboratory results showed a strongly elevated white cell count with pronounced neutrophilia and markedly raised C-reactive protein (table 1). Swabs were taken from the pustular skin lesions for culture, and two sets of blood cultures were collected. An incisional skin biopsy was taken from a pustular plaque on the right upper back for histopathology.

Pending the results of the above investigations, a provisional diagnosis of neutrophilic dermatosis (most closely resembling SS) was made, and the patient's daily prednisone 50 mg dose was substituted by intravenous hydrocortisone 400 mg daily. The condition was considered to be likely associated with the patient's underlying colitis, and since AZA-induced SS had been reported in a handful of previously published cases, therapy with AZA was interrupted. The patient responded well to intravenous steroids with flattening of his skin lesions, disappearance of the pustules and appearance of crusts covering the lesions. Simultaneously his body temperature normalized. Histopathological examination of the skin biopsy taken at onset (fig. 3) revealed marked superficial edema with florid neutrophilic infiltration in the whole dermal thickness, consistent with SS syndrome. Cultures taken prior to antibiotic therapy from blood and skin swabs were all sterile. Complete healing of skin lesions with residual hypopigmented scars occurred within 3 weeks. Given the patient's active colitis and the impossibility to further treat with AZA as a steroid-sparing agent, we decided to start infliximab on the ninth day of hospitalization both for induction and maintenance therapy. According to a telephone follow-up 1 year later, there were no recurrences of his symptoms, and his colitis was well controlled by therapy with infliximab and mesalazine.

A very recent review of the literature up to the 30th of May 2014 identified 16 reported cases of AZA-induced SS (table 2) [4–8, 10–17]. Analysis of these 16 reported cases shows an age distribution upon onset ranging from 9 to 89 years, an association of AZA-induced SS with IBD in 13 of 16 cases (81%), and an onset within the first month of AZA therapy (with an average time to onset of 33 days, range 7–330) in 15 of 16 patients (94%) (table 2). In the seven case reports in which the thiopurine methyltransferase (TPMT) levels were indicated, no deficiency in TPMT existed, making a defect in AZA methylation and metabolism unlikely, and the latter an unlikely cause of the observed neutrophilic dermatosis. Rechallenge with AZA was tested in 6 of the reported cases and was positive in

all of them, thus indicating direct causality of AZA in these cases of SS.

The pathogenesis of SS is incompletely understood. The association with underlying diseases and drugs suggests a hypersensitivity reaction, and it has been suggested that a dysregulation of cytokine release including IL-1, granulocyte-macrophage colony-stimulating factor (GM-CSF), G-CSF and interferon-γ may be involved [18, 19]. Based on reports linking IL-1β to diseases associated with neutrophilic infiltration of the skin, such as the rare genetic autoinflammatory syndrome associating pyogenic arthritis, pyoderma gangrenosum and acne, named PAPA syndrome [20], and the cryopyrin-associated periodic syndromes (CAPS) [21], we analyzed IL-1β expression levels in the skin lesions of the reported patient. As shown in figure 4, mRNA levels for IL-1β in our patient's skin biopsy assessed by quantitative RT-PCR with cDNA primers for the housekeeping gene RPL27 (forward 5′-ATC GCC AAG AGA TCA AAG ATA A-3′, reverse 5′-TCT GAA GAC ATC CTT ATT GAC G-3′) and IL-1β (forward 5′-CAC GAT GCA CCT GTA CGA TCA-3′, reverse 5′-GTT GCT CCA TAT CCT GTC CCT-3′) were over 250-fold higher than those observed in normal skin, and this was associated with enhanced expression of the mature active form of IL-1β in inflammatory cells – mainly neutrophils – of the dermal infiltrate as identified by immunohistochemistry.



Color version available online

Fig. 3. Skin biopsy taken on the upper back showing marked superficial edema with florid neutrophilic infiltration of the whole dermal thickness. Hematoxylin and eosin, ×100.

Table 1. Summary of laboratory investigation findings

Test	Result	Normal range
Hemoglobin, g/dl	9.1	13.4–17.0
White cell count, $\times 10^3$/μl	22.4	3.0–9.6
Neutrophils, $\times 10^3$/μl	20.16	1.4–8.0
Platelets, $\times 10^3$/μl	602	143–400
Sodium, mmol/l	134	136–145
Potassium, mmol/l	3.9	3.3–4.5
Urea, mmol/l	6.6	2.14–7.14
Creatinine, μmol/l	94	62–106
Albumin, g/l	27	40–49
C-reactive protein, mg/l	193	<5

Discussion

Acute febrile neutrophilic dermatosis or SS is a prototypic neutrophilic dermatosis first described in 1964 by Dr. Robert Douglas Sweet [1]. The characteristic clinical manifestations of this disorder include acute eruption of tender, red or purple-red papules, nodules or plaques, occasionally associated with pustules, bullae or ulcers, and constant systemic symptoms (pyrexia, fatigue). Together with cutaneous manifestation SS can nearly involve any organ system. Inflammation in some of these organs can cause serious long-term quality of life impairment. The sight-threatening ocular manifestations merit particular mention [22]. Cutaneous biopsies reveal an inflammatory infiltrate consisting mainly of mature neutrophils in the upper dermis.

The pathogenesis of SS is unknown. The association of the disorder with infections, IBD, drugs, autoimmune diseases and malignancies, as well as the higher incidence in women, suggest a hypersensitivity reaction [23]. One current attractive hypothesis regarding the pathogenesis of SS is a local or systemic dysregulation of cytokine secretion. Among the potentially responsible cytokines are IL-1, IL-3, IL-6, IL-8, G-CSF, GM-CSF and interferon-γ [18]. Elevated serum levels of IL-1, IL-2 and interferon-γ, but not IL-4, suggest that the expression of Th1 cytokines may be involved in the pathogenesis of this syndrome [18].

SS does fulfill the current criteria for classification as an autoinflammatory disease [24]. Autoinflammatory diseases are a relatively new category of diseases distinct from allergic and autoimmune diseases and characterized by seemingly unprovoked recurrent inflammation in the absence of evidence of circulating autoantibodies or an antigen-specific T cell response [25]. Genetic mutations affecting proteins of the inflammasome complex or proteins that regulate the function of the inflammasome have been found in several of the autoinflammatory syndromes. In-

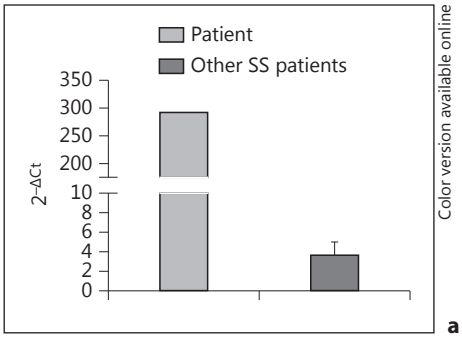
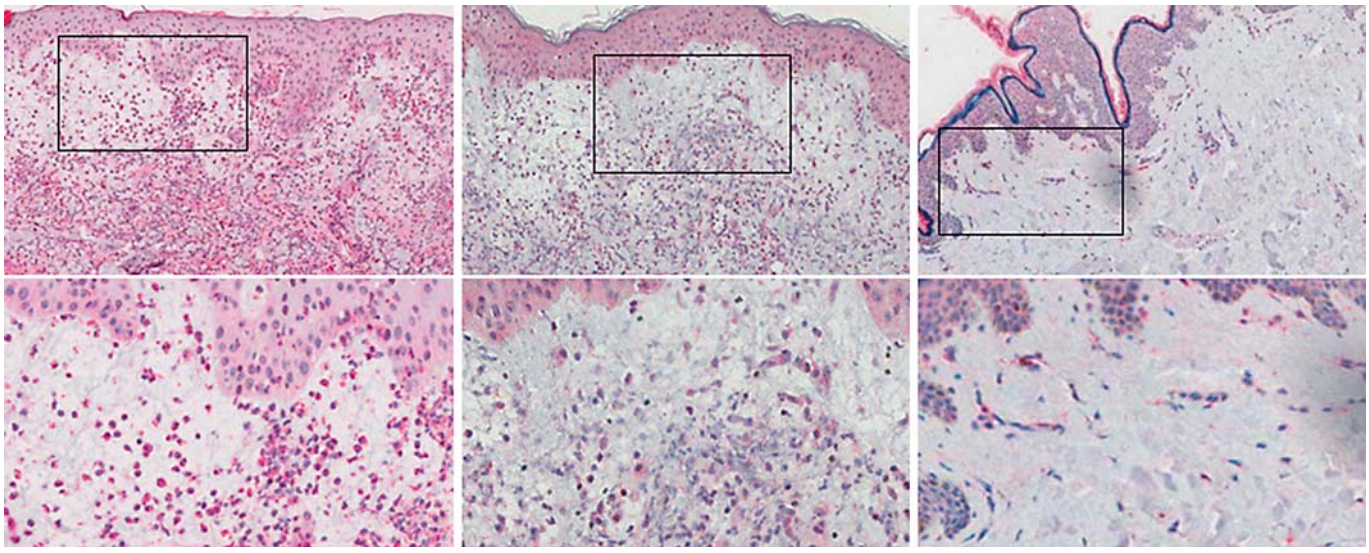


Fig. 4. a Analysis of IL-1β mRNA levels by quantitative RT-PCR in the patient's skin biopsy and healthy control skin. **b** Immunohistochemical stainings with an anti-IL-1β antibody and with an appropriate isotype control antibody were performed on the patient's skin biopsy and compared to anti-IL-1β antibody staining in healthy control skin.



Patient skin, anti-IL-1β Ab | Patient skin, isotype control Ab | Healthy control skin, anti-IL-1β Ab

Table 2. Reported cases of AZA-induced SS

Case No. [ref.]	Age, years/ sex	Underlying disease	Time of onset after starting AZA	Recurrence with rechallenge	TPMT level	Concurrent steroid use
1 [8]	9/F	ulcerative colitis	10 days	no rechallenge	N	yes
2 [4]	39/F	Crohn's disease	28 days	yes	N	yes
3 [4]	33/M	systemic lupus erythematosus	14 days	no rechallenge	N	yes
4 [14]	46/M	ulcerative colitis	14 days	yes	NR	yes
5 [6]	49/M	ulcerative colitis	11 months	yes	NR	yes
6 [7]	32/M	Crohn's disease	7 days	yes	above ref. range	yes
7 [7]	68/M	myasthenia gravis	10 days	no rechallenge	above ref. range	yes
8 [7]	42/M	ulcerative colitis	14 days	no rechallenge	NR	yes
9 [13]	89/F	bullous pemphigoid	18 days	no rechallenge	N	yes
10 [11]	45/M	Crohn's disease	14 days	yes	NR	yes
11 [12]	55/M	Crohn's disease	7 days	yes	NR	yes
12 [10]	53/M	ulcerative colitis	7 days	no rechallenge	NR	yes
13 [15]	50/M	indeterminate colitis	14 days	no rechallenge	NR	yes
14 [17]	75/M	Crohn's disease	14 days	no rechallenge	NR	no
15 [5]	81/F	Crohn's disease	14 days	no rechallenge	NR	yes
16 [16]	51/M	Crohn's disease	10 days	no rechallenge	N	yes

F = Female; M = male; N = normal; NR = not reported.

flammasomes are a group of protein complexes that recognize a diverse set of pathogen- and/or danger-associated inflammation-inducing stimuli and that control the production of important proinflammatory cytokines such as IL-1β and IL-18 [26]. Mutations in inflammasome components may result in overactivity of the inflammasome or failure to limit IL-1-mediated inflammation, as is the case in CAPS such as Muckle-Wells syndrome that are due to activating mutations of the inflammasome component NLRP3. In a large number of autoinflammatory diseases, systemic corticosteroids have only modest effect. Biologic agents such as anakinra (Kineret®), a recombinant IL-1R antagonist, can result in a dramatic and consistent improvement in those syndromes where a clear link to IL-1 has been shown [27]. Likewise therapy with canakinumab, a human monoclonal antibody targeted at IL-1β, has been shown to induce rapid, durable and complete clinical responses in 97% of CAPS patients studied [28]. Our data showing very high levels of IL-1β mRNA and protein in the skin lesions of our patient are supportive of the above notion that SS is an autoinflammatory disease, and suggest that IL-1β may contribute to the neutrophilic infiltration of the skin and fever that characterize SS. According to the recently updated classification of autoinflammatory disease, our case is a type 1, complex/acquired autoinflammatory disease [25].

Prednisone or prednisolone at an initial dose of 0.5–1.5 mg/kg body weight/day, with gradual tapering over 2–4 weeks, represents the standard first-line treatment for SS. In recurrent disease, therapy with colchicine, potassium iodide, dapsone, doxycycline, non-steroidal anti-inflammatory agents and cyclosporine has been described, with mixed results [29]. A few case reports mention successful use of infliximab (5 mg/kg) on a compassionate use basis in refractory SS. Evidence for any of these therapeutic regimens is however limited as based on case reports and small case series. Recently very encouraging responses to Kineret have been reported in patients with refractory SS, further suggesting that IL-1α or IL-1β play a significant role in the pathophysiology of this disease [30, 31].

One of the more frequently reported diseases associated with classical SS is IBD. Benton et al. [32] described its association with ulcerative colitis for the first time in 1985. Since then, a large number of case reports have confirmed this association [32–46]. The association of SS with Crohn's disease is less common, with fewer than 40 cases described in the literature. SS associated with IBD tends to be more common in women (87%) and is usually associated with active disease [47]. The presence of extraintestinal symptoms, such as joint symptoms and other skin manifestations, is frequent in patients with IBD-associated SS [48]. As mentioned earlier, SS may be also associated with medications [2], the administration of G-CSF being responsible for the majority of drug-induced cases of SS. Many patients with IBD are treated with AZA as a corticosteroid-sparing agent. When SS occurs in such patients, IBD is the first suspected cause of the syndrome, given the well-reported association [10, 15]. However, in the last few years several papers reporting a possible association between AZA and SS have been published (table 2) [4–8, 10–17]. Interestingly, two of the cases reporting AZA-associated SS had an underlying disease other than IBD, and rechallenge of patients with AZA reproduced SS lesions in all 6 cases rechallenged, both facts providing support for a potential role of AZA as a trigger/co-factor in certain cases of SS [4, 7].

The AZA hypersensitivity syndrome, which typically occurs within the first 4 weeks of initiation of AZA therapy [9] and is characterized by systemic symptoms identical to those of SS (fever, leukocytosis, malaise, arthralgia), was considered to be the cause in many of these cases (table 2). A review of the English language literature by Bidinger et al. [4] showed that about 50% of patients with a hypersensitivity reaction to AZA had cutaneous manifestations. The majority thereof had biopsy or clinical features consistent with a neutrophilic dermatosis. Interestingly, withdrawal of AZA and rechallenge with the drug indicated that at least in some of the abovementioned cases [4, 6, 7, 11, 12, 14], a direct association between AZA and SS existed. In another case, on the other hand, the AZA dose was increased and the rash eventually resolved [41]. As the systemic manifestations described for AZA hypersensitivity syndrome have all also been reported to occur with varying frequencies in SS, it is presumed that both denominations refer to variants of the same disease [49, 50].

Our patient with SS developing 14 days after initiation of AZA therapy for active IBD meets all of the diagnostic criteria for drug-induced SS as presented by Walker and Cohen in 1996 [51]. Especially the localization and the clinical outcome arguments against the presence of an AZA hypersensitivity syndrome. The latter tends to favor the lower extremities and most cases resolve within 2–3 days after withdrawal of the medication and may not necessitate an increase in corticosteroid dose. In view of the impressive clinical presentation resulting in permanent skin scarring, rechallenge with AZA as a proof of causality was not performed. Full resolution of clinical symptoms occurred upon therapy with systemic steroids and infliximab. Our data showing involvement of IL-1β in SS, taken together with reports of successful therapy of SS with the IL-1 receptor antagonist anakinra, suggest that IL-1 plays a role in the pathogenesis of SS, and the latter therapy may be optimal in steroid-refractory cases of SS. However, anakinra was not shown to be effective in IBD. For that reason a different strategy was chosen in the patient discussed here.

Disclosure Statement

The authors have no conflict of interest to declare. There was no funding source.

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